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ABSTRACT

Pd-catalyzed allylations of cyclic bis-allylic substrates, carried out either as two separate steps or in a pseudo-domino fashion, can generate 2-carboxyl-hexahydroindoles bearing an unsaturation in different positions. Sequential homologation, and epoxidation or *syn*-dihydroxylation steps were investigated to access analogues of the bicyclic 2-carboxyl-6-hydroxyoctahydroindole motif of aeruginosins, a family of peptides displaying serine protease inhibitor activity..

Introduction

Aeruginosins[1] constitute a family of structurally related molecules found in cyanobacteria (blue-green algae). These peptidic structures that incorporate the 2-carboxyl-6α-hydroxy-octahydroindole (CHOI) bicyclic structure hydroxylated in 5 and / or 6 positions, display inhibitory actions against several serine proteases such as thrombin and trypsin (Figure 1).[2] Since the discovery of their potent anticoagulant action, structure-activity relationship (SAR) studies on aeruginosin family are constantly and intensively pursued.[3] Although synthetic routes of some of these structures have been recently reported, further studies are still desirable, especially those focusing on the common bicyclic CHOI fragment and access to analogues of it.

Some years ago, we anticipated that analogues of the CHOI motif could be ideal targets, achievable through palladium chemistry developed in our laboratory.[4,5] In the present study we developed a double Pd-catalyzed allylation (amination and alkylation) of the cyclic bis-allylic substrate **I**, which, as a function of the *modus operandi*, provided the desired bicyclic advanced intermediates **II** and **III** that differ by the double bond location (Scheme 1). After an appropriate one-carbon homologation at position 2, diastereoselective post-functionalizations (epoxidation and *syn*-dihydroxylation) of the resulting hexahydroindoles **IV** and **V** were carried out to evaluate the selectivity of these transformations, which provide CHOI analogues as a function of the transformation and the position of the unsaturation.

Results and discussion

"Separated allylations" strategy-based approach to the bicyclic tetrahydroindolone 6.

This strategy is based on the construction of the bicyclic tetrahydroindolone structure **6** starting from 1,3-cyclohexadiene **1**. This was achieved through a five-step sequence (Scheme 2), as previously described by us.[4b] Two key steps of this synthetic sequence are based on palladium catalysis. First, 1,3-cyclohexadiene **1** was converted into the corresponding chloroacetate ***cis*-2** according to Bäckvall's protocol.[6] Then, palladium-catalyzed allylation of *p*-methoxybenzylamine with the allylic chloride *cis*-**2** afforded *cis*-**3**. Standard treatment of this amine with methyl 3-chloro-3-oxopropionate gave the 1,4-disubstituted amide *cis*-**4**, which underwent a smooth intramolecular allylic alkylation. Two different palladium-based catalytic systems can be used, both leading to bicyclic lactam **5** in 80% as a single diastereoisomer.[7] Finally, demethoxycarbonylation of **5** under Krapcho conditions[8] led to lactam **6**.

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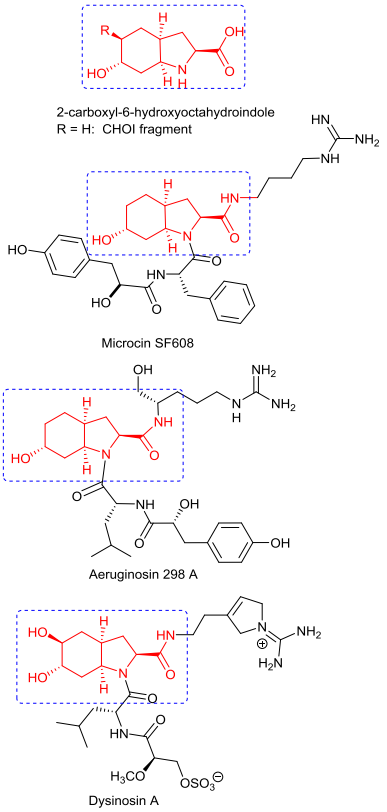
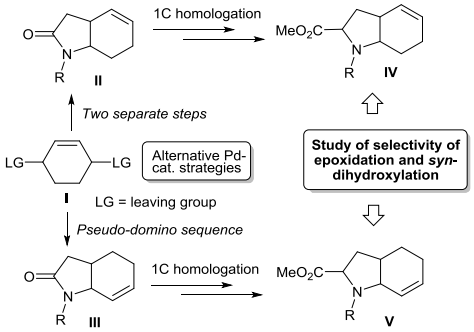
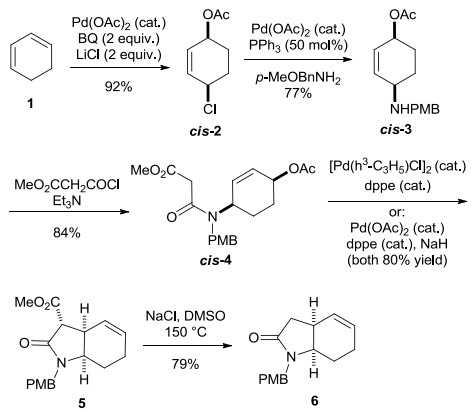


Figure 1. CHOI motif and representative members of the Aeruginosin family.



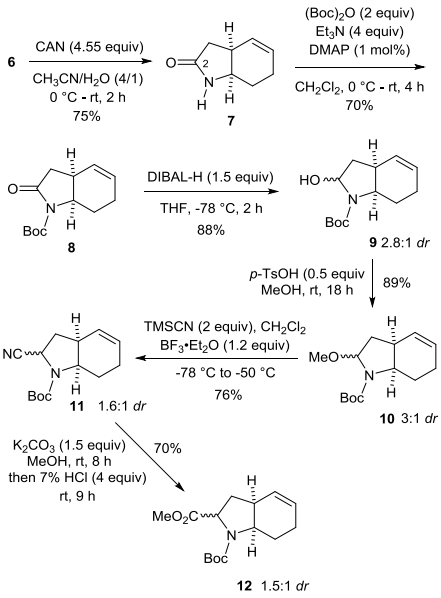
Scheme 1. CHOI aim of the project.



Scheme 2 Previous synthesis of the bicyclic tetrahydroindolone **6**.

Transformation of lactam 6 to the methoxycarbonylated derivative 12.

Introduction of the carboxyl substituent at position 2 of the hexahydroindole bicycle was planned through α-aminoether homologation. However, this type of strategy is viable only when the nitrogen atom of the aminoether function is electron poor. Accordingly, a PMB-to-Boc *N*-protection switch was accomplished through treatment with CAN, followed by standard Boc protection of the resulting secondary amide **7**. DIBAL-H reduction of **8** led to hemiaminal **9**, whose treatment with MeOH in presence of a catalytic amount of *p*-TsOH gave the desired *N*,*O*-acetal **10** as a 3:1 diastereomeric mixture. C1-homologation was achieved through trimethylsilylcyanide (TMSCN) addition to **10** in the presence of $BF_3{\cdot}Et_2O$.[9] Finally, nitrile methanolysis[10] (K_2CO_3, MeOH, rt; then 7% HCl) gave methyl ester **12** as an inseparable 1.5:1 diastereoisomeric mixture (Scheme 3).[11]



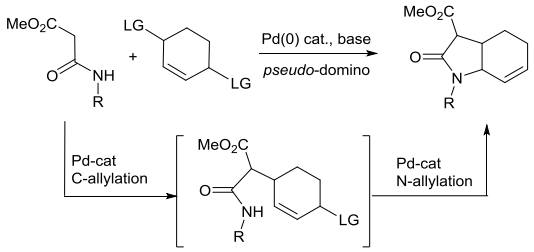
Scheme 3. Synthesis of the methoxycarbonylated derivative **12**.

Different epimerization attempts, in the hope of obtaining a single (or at least highly prevalent) diastereoisomer of **12** were carried out. However, treatment of ester **12** with catalytic amount of DBU at room temperature or reflux (in the aim of reaching the thermodynamic regime), or treatment with a stoichiometric amount of a lithium amide (LDA or $LiNEt_2$) followed by kinetic quenching, led only to recovered starting material with unchanged diastereoisomeric ratio, or degradation products. Furthermore, preliminary studies of epoxidation of intermediate **6** showed to be rather non-selective (*dr* = 1.3:1),[12] while epoxidation and dihydroxylation of diastereomeric mixtures of **11** (*dr* = 1.6:1) and **12** (*dr* = 1.5:1) under various conditions gave complex products/diastereomers.[12]

Judging that unsaturation at position 4,5 of the hexahydroindole bicycle was likely intrinsically unbiased for diastereoselective functionalizations, we passed to tackle an alternative way of generating this bicyclic unit, so as to obtain the unsaturation at position 6,7. This objective was achieved through a modified palladium-catalyzed strategy, featuring this time a domino sequence.[13]

Domino sequence-based approach to *N*-tosyl bicyclic tetrahydroindolone 17

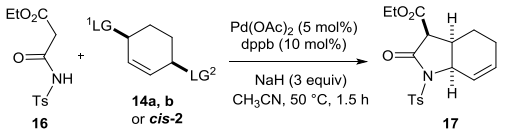
This second strategy exploits the double Pd-catalyzed allylation of a malonamide with a cyclohexenyl bis-allylic system, according to a *C*-allylation/ *N*-allylation *pseudo*-domino[14] sequence (Scheme 4).[15]



Scheme 4. Palladium-catalyzed *C*-allylation / *N*-allylation domino sequence.

N-Tosyl malonamide **16**[16] was selected as the appropriate C/N double nucleophile, and its reaction with *cis*-OBz cyclohexene *cis*-**14a** using conditions similar to those adopted by Mori[15] were first tested (Table 1). In particular, use of NaH (3 equiv.) as the base, gave the bicyclic product **17**[17] in 67% yield (Table 1, entry 1). This result confirms that malonamides are effective C/N bis-nucleophiles for η^3-allyl palladium chemistry. Moreover, as the unsaturation in **17** is found at position 6,7, it follows that the carbanionic site reacts before the nitrogen atom in the domino sequence.[18] Other cyclohexenyl *cis* bis-allylic systems were then tested. Diacetate *cis*-**14b** gave the corresponding bicyclic product **17** in 52% yield (Table 1, entry 2), while the chloroacetate ***cis*-2** intermediate smoothly led to 79% yield (Table 1, entry 3).

Table 1. Palladium-catalyzed bis-allylation of the *cis*-OBz cyclohexene with *N*-tosyl malonamide.[a]

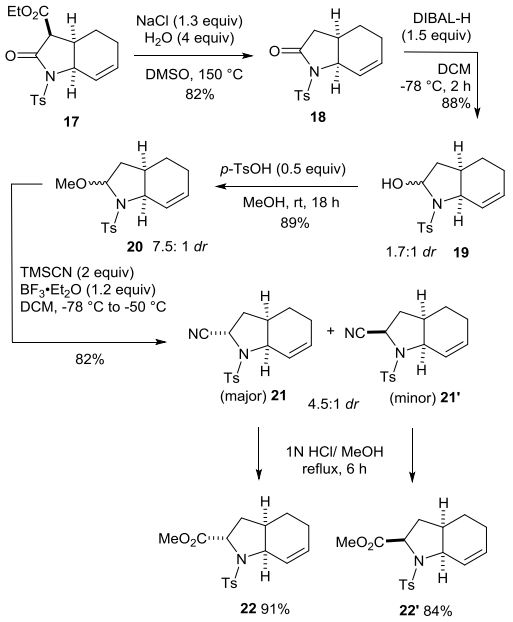


Entry	LG^1	LG^2	**14** or ***cis*-2**	**17** (%)
1	OBz	OBz	**a**	67[a]
2	OAc	OAc	**b**	52
3	Cl	OAc	***cis*-2**	79

[a]Switch to K_2CO_3 (3.0 equiv.) afforded 45% yield of **17**, while no product could be obtained without base.

Transformation of *N*-tosyl lactam 17 to the epimeric methoxycarbonylated derivatives 22 and 22'.

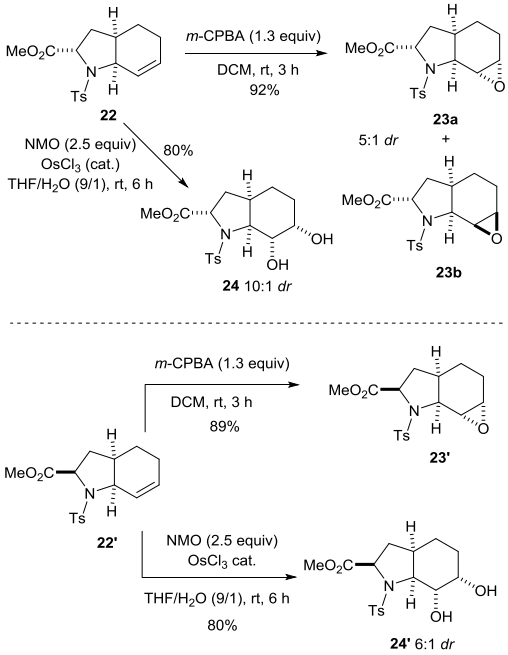
The 6,7-unsaturated bicyclic structure **17** was then processed in the same way as described previously for the 4,5-unsaturated one, so as to obtain the corresponding 2-methoxycarbonylated derivative. In this case, demethoxycarbonylation to give **18**, followed by reduction to hemiaminal **19**, formation of the *N*,*O*-acetal **20**, and cyanide homologation afforded nitriles **21** and **21'** in 4.5:1 ratio, which are easily separated by chromatography. Finally, separate acidic methanolysis of the two epimeric nitriles gave the two corresponding methyl esters **22** and **22'**.[19] Gratifyingly, all the steps of this synthetic sequence turned out to be high yielding (Scheme 5).



Scheme 5. Synthesis of the epimeric methoxycarbonylated derivatives **22** and **22'**.

Stereoselective epoxidation and *syn*-dihydroxylation of 2-methoxycarbonyl hexahydroindoles 22 and 22'

Then, standard epoxidation and *syn*-dihydroxylation of the two separated epimeric bicyclic structures **22** and **22'** were tested. In the event, treatment of the major epimeric ester **22** with *m*-CPBA led to a 5:1 ratio of epoxydes **23a** and **23b**, whereas under the same conditions the minor one **22'** reacted in a totally stereoselective way, affording epoxyde **23'** as a single isomer (Scheme 6, arrows in top right direction). Finally, separated *syn*-dihydroxylation of **22** and **22'** with $OsCl_3$ (cat.)/ NMO[20] gave the two *syn*-dihydroxylated products **24** and **24'** in good yields and interesting diastereoselectivities (Scheme 6, arrows in bottom right direction). The configurations of major diastereoisomers were confidently assigned via ^{1}H NMR NOESY and coupling constant analysis.



Scheme 6 Stereoselective epoxidation and *syn*-dihydroxylation of 2-methoxycarbonyl hexahydroindoles **22** and **22'**.

The above results indicate that while the double bond in substrate **12** appears to be unbiased toward the tested electrophilic reagents, substrates **22** and **22'** show a constant and strong preference to react through the least hindered face. Analysis of the substrates indicates that the allylic stereogenic centre of the cyclohexenyl ring, which is in close proximity to the reacting π-system, carries a tiny CH_2 substituent in the case of **12**, while that position is occupied by a bulky *N*-Ts moiety in the case of substrates **22** and **22'**. The above difference, which in turn correlates with the conformational populations adopted by the respective substrates, may account for the dramatic selectivity difference shown by these two substrates (Figure 2).

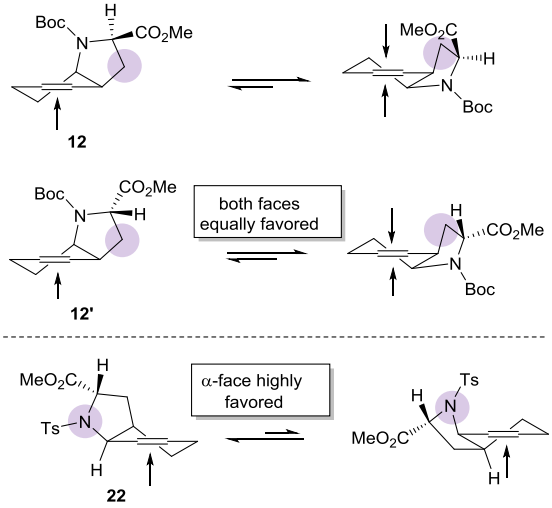


Figure 2. Comparison of selectivity of epoxidation and *syn*-dihydroxylation between substrates **12** and **22** (and **22'**) differing in the position of the unsaturation. The substituent of the allylic stereogenic centre is highlighted with a circle.

Conclusions

In summary, we have developed a synthetic sequence to reach analogues of the CHOI unit. The first steps of the synthetic sequence are a *C*-allylation and an *N*-allylation, both Pd-catalyzed, which convert a cyclic bis-allylic substrate into a hexahydroindole structure. In particular, depending on the selected *modus operandi* - two separate steps *versus* a single pseudo-domino sequence - the unsaturation of the resulting hexahydroindole structures ends-up at different positions. After one-carbon homologation, epoxidation or *syn*-dihydroxylation of the resulting isomeric bicyclic advanced intermediates allowed to establish that unsaturation at 6,7 is more biased for diastereoselective electrophilic transformations to reach CHOI analogues. These results should be of relevance for future studies on aeruginosins synthesis and CHOI analogues.

Acknowledgments

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7. The coupling constant values in the ^{1}H NMR spectrum of the bicyclic products indicates the presence of a *cis* junction between the two rings, and a *trans* disposition between the ester function and the carbon atom of the 6-membered ring directly bound to the vicinal position. This assignment is in agreement with previous work by us and others. See: 4b; Ikeda, M.; Teranishi, H.; Nozaki K.; Ishibashi, H. *J. Chem. Soc. Perkin Trans. 1* 1998, 1691–1698.
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9. The C1-homologation was also tested directly on the carbinolamine **10** with TMSCN in presence of boron trifluoride etherate. However, the desired cyano derivative **11** was obtained in low yield (~30%).
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11. Several nitrile methanolyses were tested before founding the satisfactory one. In particular, the system (TMSCl, MeOH) and (10N NaOH, MeOH) brought about simultaneous deprotection of the *N*-Boc protecting group and/or degradation.
12. Epoxidation of **6** with *m*CPBA produced an inseparable diastereomeric mixture in a 1.3:1 ratio with a combined yield of 83%, while epoxidation or dihydroxylation of the diastereomeric mixtures of **11** and **12** yielded intractable mixtures of products or undistinguished diastereomeric mixture. For more details, see supporting information (S44-47).
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17. The coupling constant values in the ^{1}H NMR spectrum of the products suggest again the presence of a *cis* junction between the two rings. However, in this case a *trans* disposition between the ester function and the hydrogen atom of the junction is observed ($J^3_{cis} \approx 12$ Hz whereas $J^3_{trans} \approx 7$ Hz).
18. Unpublished experiments carried out in our laboratories indicate that the acidic carbon of these malonamides reacts constantly before the nitrogen atom in these domino sequences, irrespectively of the nature of the nitrogen protecting group, as well as of the equivalents of base used.
19. The relative stereochemistry of **21**/**21'** and **22**/**22'** were ascertained by ^{1}H NMR NOESY and coupling constant analysis, and compared with NMR structural analysis already described in

literature for this kind of structure (ref. 3a,d). See also: Nuhrich A.; Moulines, J. *Tetrahedron* **1991**, *47*, 3075–3088.

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